Influence of blister packaging on the efficacy of artesunate + mefloquine over artesunate alone in community-based treatment of non-severe falciparum malaria in Myanmar

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Three studies were carried out to determine the need, acceptability, and efficacy of adding mefloquine to artemisinin derivatives (AD) for the first-line treatment of uncomplicated falciparum malaria. The first was a retrospective study of 255 basic health workers which showed that their recommendation of AD to patients depended on their level of training. None of the paramedics/midwives and only 9% of 129 doctors had prescribed AD, and no one had recommended AD in combination with mefloquine; 72% of patients used courses that were too short for parasitological cure. To promote the addition of mefloquine to AD regimens we conducted intervention workshops with health care providers and subsidized the cost of mefloquine to patients. In the second study, we interviewed 200 patients before and after the intervention to evaluate drug compliance with full doses of AD and use of subsidized mefloquine. After the intervention, we found that only 3.6% had used mefloquine and 62% had taken non-curative doses of AD. In the third study, we provided blister packs of medication in daily doses and compared the intake of AD + placebo (158 patients) with that of AD + mefloquine (222 patients) for 5 days. The compliance with both regimens was 99%. Blood smears for parasites on day 28 showed one positive in the AD + mefloquine group and 7 positive in the AD group. We conclude that provision of blister packs of daily doses is a very effective way to improve compliance with short courses and drug combinations, but the efficacy of the combination in Myanmar in this particular study was only marginally higher than that of AD alone.

Introduction

Artemisinin derivatives (AD, i.e. artemether injections, artesunate injections, and artesunate tablets) have been shown to be effective in the treatment of severe *Plasmodium falciparum* malaria in south-east Asia. Unfortunately, these compounds have a high recrudescence rate (up to 25–40%) even when used for the recommended 5 days to treat uncomplicated malaria cases. Although these compounds have recently become widely available in Myanmar, prescribing practices of health workers and the compliance of patients with uncomplicated malaria have not been studied. This information is needed to develop strategies for the control and rational use of these drugs in order to preserve their effectiveness in treating severe and complicated falciparum cases, especially in areas of multidrug-resistant malaria.

In 1994 a hospital-based study in Myanmar showed that a 7-day treatment using oral dihydroartemisinin (Cotecxin) was 100% efficacious against nonsevere malaria (*1*); there was no recrudescence in any of the 30 patients who were followed up for 28 days. As for compliance, another study of 20 outpatients with non-severe malaria showed that 25% discontinued when the symptoms cleared and did not finish the full course (*2*, *3*). It was considered unreasonable to expect 7 days of compliance, and when 3- and 5-day regimens were examined the cure rates fell to 84% and 89.5%, respectively. Resistance to mefloquine, the third-line drug in most of Myanmar, has been documented in many areas of South-East Asia. Along the Thai–Myanmar border, for example, 41.7% of patients have been reported to be resistant to mefloquine *in vivo* (*4*). However, there is no reported resistance to the combination artesunate and mefloquine (*5–7*). We therefore considered promoting the addition of mefloquine to artesunate regimens in order to decrease the probability of recrudescence and retard the spread of mefloquine resistance (*8–11*).

The following studies were conducted in sequence:

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1. *Use of artemisinins*: a retrospective study to characterize current use and conditions for the use of artemisinin derivatives.

2. *Subsidized mefloquine intervention*: to promote the use of a combined artesunate + mefloquine regimen for uncomplicated malaria by educating health care providers and subsidizing the cost of mefloquine to patients.

3. *Packaging intervention*: to improve the compliance with artesunate + mefloquine by packaging and distributing them together in blister packs.

Use of artemisinins

Methods

This retrospective study to evaluate current use of artemisinin compounds in Myanmar was conducted in the following areas:

— two townships with a high prevalence of malaria (Pyin Oo Lwin and Myit Kyi Na);

— one township where drug resistance is common (Mawlamine);

— one township in central Myanmar (Thayarwady);

— one township with a low prevalence of malaria (Maubin); and

— one township with a large migrant population close to jade mines (Moekaung).

Questionnaires on the use of artemisinins were prepared for interviews with the following individuals: hospital doctors and general practitioners in the townships; nurses, health assistants and midwives; auxiliary midwives and voluntary health workers; drug store owners in the townships; and former hospital patients who had experienced severe and complicated malaria. Meetings with the hospital doctors and general practitioners were held through the various branches of the Myanmar Medical Association, at which the questionnaires were distributed and filled in by the doctors. A similar exercise was repeated with the nurses and paramedical workers in the townships. A coverage of approximately 80% of all doctors and nurses from the specified townships was obtained.

Results

A total of 129 doctors were interviewed. Artemisinin compounds were prescribed as first-line treatment by 9.1% for uncomplicated malaria, 37.6% for malaria with complications, 33% for drug-resistant malaria, and 11.9% for reasons not directly related to malaria (e.g. requested by the patient). Most doctors did not prescribe full courses, mainly because of the cost of the drug. Artemisinin derivatives alone were felt to be effective and the doctors considered they had no reason to add mefloquine to prevent recrudescence. Many doctors indicated that they did not know the dose and toxicity of the drugs (28.9%) or have information on their clinical efficacy (16.5%).

A total of 255 basic health workers were interviewed. Approximately 50.6% were aware of artemisinin derivatives and 20% had used them in treatment, with 27.5% of such use being for patients with uncomplicated malaria.

Paramedical health workers, auxiliary midwives and voluntary health workers all prescribed chloroquine, sulfadoxine–pyrimethamine, and quinine for malaria treatment. The majority of drug store owners (71 were interviewed) stocked artemether injections, 38% stocked artesunate injections, and 78.9% stocked oral artesunate tablets. Artemether injections were sold at the average price of 605.6 kyats per box of eight ampoules (US$ 1 = 600 kyats). Artesunate blister strips were sold at an average price of 129 kyats each (US$ 0.20). Artemether was also sold as single ampoules in 95.8% of shops, and 71.8% of purchases were by relatives of patients.

Hospital patients with severe and complicated malaria were mostly treated with quinine injections, but a significant number (22.6%) were treated with artemether injections. One-fifth of all patients used artesunate tablets following discharge.

Discussion

The total number of patients treated by the doctors interviewed during the study was 9000–10000 per month, about one in every ten of whom received artemisinin compounds. The majority prescribed doses that would not prevent recrudescence, i.e. short regimens and without mefloquine.

Subsidized mefloquine intervention

Methods

The objective of this intervention was to subsidize mefloquine prices in the hope that this would encourage its addition to short courses of artesunate for treatment of uncomplicated falciparum malaria. This combined regimen was promoted through workshops for doctors (public and private practitioners) and basic health workers. A questionnaire was

devised to assess their knowledge of treatment with the artemisinin derivatives, after which they were provided with verbal and written information on the treatment of uncomplicated malaria with artemisinin and mefloquine.

Mefloquine tablets were subsidized through vouchers for patients and made available in the hospital and government clinics and rural health centres to doctors and basic health workers. The latter were asked to inform each patient who was prescribed oral artemisinin preparations to take these drugs with mefloquine, which would be available on presentation of the voucher at the subsidized price at the specified outlets.

Both before and after the intervention, a random cohort of 200 patients (100 from a rural area and 100 from an urban area) who had sought advice from the workshop-trained doctors and basic health workers were followed up at home with the help of a health assistant to determine the drugs taken for treatment, the advice they received, and whether they used mefloquine.

Results

Before the intervention, 72% of all patients treated with the artemisinins had used less than the full regimen, and never in combination with mefloquine. Of the 200 patients surveyed before the intervention, 10% had been treated by hospital doctors, 58% by general practitioners, and 4% by nurses while 28% had bought the artemisinin derivatives over the counter. Of those patients who went to the doctors (in public or private practice), none had taken mefloquine.

After the intervention, 1780 packets of artesunate and no mefloquine were sold through the non-subsidized outlets. Of those dealers who kept records, 20% of the artemisinins sold had been prescribed by doctors, 11% by basic health workers, 59% by traders and 10% by patients for self-treatment; 46% of those who bought the artemisinins were given a voucher for mefloquine to be redeemed at the specified outlets, but no one took up this option. Only in the case of the hospital pharmacy, where both artesunate and mefloquine were available, did 100% of the hospital patients buy the full course of artemisinins plus mefloquine; this group constituted 3.6% of the total sample of patients treated for malaria. Compliance with the full 5-day regimen of artesunate was 62%.

The reasons given for not using mefloquine in combination with the artemisinin derivatives were inconvenience (owing to distance) of redeeming the voucher for mefloquine at the specified outlets, confidence in artesunate monotherapy, and lack of funds to purchase mefloquine even at the subsidized price. Through interviews with patients, we learned that cost was not a significant factor hindering the purchase of mefloquine; however, its non-availability at the same outlets that sold artesunate was a constraint against combined therapy.

Discussion

Our results indicate that special packaging for both artesunate and mefloquine would ensure that both drugs were always sold and taken together. This advantage to patients could more than make up for the higher expense (at the unsubsidized price of mefloquine) because of the convenience if one had to use combined treatment.

Packaging intervention

The objective of this study was to examine the effectiveness of a combined package (5-day course of artesunate + mefloquine) in increasing compliance to both drugs and in reducing the malaria recrudescence rate.

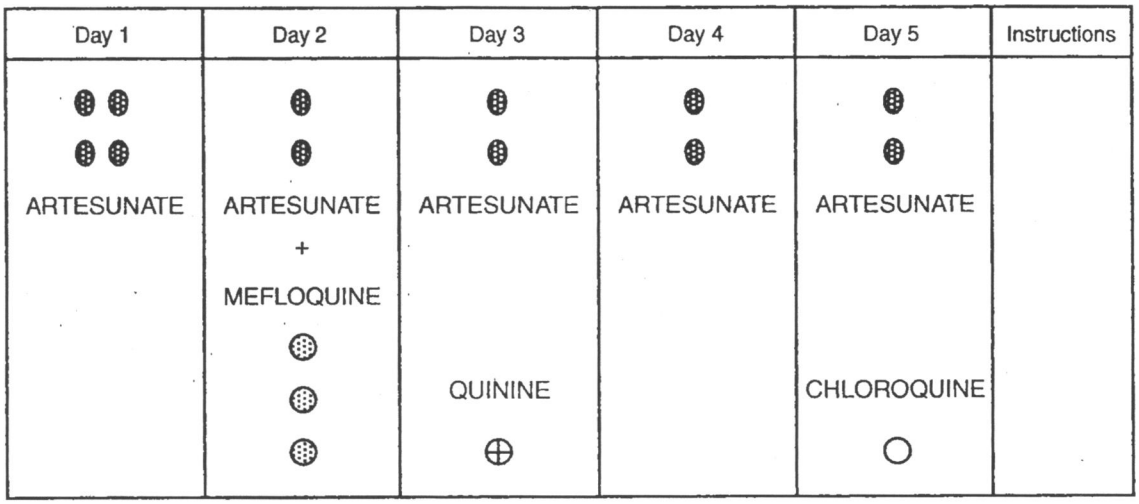
The packaging of the 5-day course was consumer friendly and consisted of a large transparent packet with five transparent strips, each containing the daily dose, marked day 1 to day 5. The dose for the second day included either mefloquine or a placebo. An instruction leaflet in simple Burmese was included in the package explaining the regimen and the daily dose to be taken.

A pre-intervention study assessed the willingness of dealers in Bago township to sell these packets of antimalarials and the patients' acceptance and understanding of the packaging and instructions. This was followed by a larger double-blind study in six rural health centres, 160 km from Yangon, to assess and compare the efficacy of 5-day regimens of oral artesunate + mefloquine and of artesunate alone in the community setting. In addition, the study assessed the patients' compliance rates using the new packets and compared them with those obtained previously (studies 1 and 2 above).

Methods

Six rural health centres (RHC) in a malaria-endemic area within 160 km of Yangon were selected on the basis of their willingness to participate, and their capacity to complete the study. Each centre had 4–5 subcentres run by a midwife, each one serving 3–5 villages with 500–1000 inhabitants in each. All six

Fig. 1. **Example of a blister pack for a 5-day course of artesunate + mefloquine including markers.**



centres had similar malaria transmission seasons and transmission patterns, as well as similar demographic and occupational features.

The drug packets were prepared, with daily dosages, as follows (Fig. 1):

— day 1: 4 tablets artesunate;

— day 2: 2 tablets artesunate and 3 tablets of mefloquine (intervention group) or paracetamol (control group);

— day 3: 2 tablets artesunate and one tablet of quinine (as a marker of compliance);

— day 4: 2 tablets artesunate; and

— day 5: 2 tablets artesunate and one tablet of chloroquine (as a marker of compliance).

Compliance on days 3 and 5 was measured through a urine sample taken on day 7.

The blister packets were sold at the six health centres. The Intagaw and Gyogone RHCs (intervention group) received the blister packs containing artesunate and mefloquine, while the other four RHCs (control group) received artesunate with paracetamol as the placebo. The paracetamol and mefloquine tablets were indistinguishable, and the health centres were not told which group they were in. Drugs were sold at full price, with no difference in price between the placebo and combined drug packets.

The criteria for inclusion in the study (both intervention and control groups) were patients aged >12 years who attended the RHC's outpatient clinic, who had a slide-confirmed (nonsevere) *P. falciparum* infection, and who had taken no antimalarial medication during the previous 7 days. The study was explained to the eligible patients; those who consented to participate purchased the medication (blister packs), the use of which was explained to each patient by the health assistant.

A total of 60 private practitioners, 90 basic health staff, and 10 dealers from the two townships, where the six RHCs were located, were recruited to participate in the pre-intervention training. Each participant was given information verbally, and in booklets, on how to prescribe or sell the blister packs. The booklets (in English for the physicians and in Burmese for the dealers and local health staff) were distributed free. They were instructed to advise all patients to buy the entire blister pack and to take all the tablets; each pack contained instructions in simple Burmese on the importance of compliance with the full course. The number of sales was recorded. At the end of the study, 300 blister packs were sold through the ten shops chosen by the township medical officer. There were no adverse comments from either the drug sellers or malaria patients. All patients were informed that the treatment regimen was artesunate with or without mefloquine.

Table 1: **Comparison of efficacy of artesunate + mefloquine against artesunate alone**

Treatment and place	No. of subjects screened	No. +ve for *P. falciparum*	No. at 28 days	No. with positive smear on: Day 7	Day 28	Remarks
Artesunate + mefloquine:						
Intagaw	329	205	205	2	1 *P.f.*	1 patient hospitalized (giddiness) 5 patients with some giddiness
Gyogone	35	17	17	0	0	
Subtotal	364	222	222	2	1	
Artesunate + placebo:						
Phayagyi	243	165	115	0	7 *P.f.*	1 patient hospitalized (vomiting)
Sarbutaung	44	22	14	0	0	
Kyaunta	80	26	17	0	0	
Pyinbonegyi	35	20	12	0	0	
Subtotal	402	233	158	0	7	
Total	766	455	380	2	8	

Each *Plasmodium falciparum* slide-positive patient who purchased the blister pack from the RHCs was followed up at home on day 7 and day 28 by the respective RHC health assistants, and the parasitological status was assessed on each day by blood smears. On day 7, patients were also interviewed regarding treatment compliance — i.e. completing the prescribed course — and asked to show any remaining tablets. Finally, a urine sample from each patient was taken for subsequent analysis of the presence of chloroquine (Lelijveld–Kortmann test) and quinine (Mayer–Tanret reagent test) (*12*).

For the calculation of statistical power and sample size, the mefloquine group was expected to have a 100% cure rate; the failure rates in the placebo group, which we considered useful to detect, was expected to be greater than 15%. The minimum sample size for each of the two groups ($P = 0.95$, power = 0.20) was calculated to be 60; total sample size was therefore 120. However, a much larger number were screened to make up for negative smears or *P. vivax* malaria and for loss to follow-up on days 7 and 28.

Results

Over the 7-month study period, April to October 1996, a total of 766 subjects were screened for entry; 455 were confirmed smear-positive for *P. falciparum*, 107 for *P. vivax*, and 3 for mixed infections. A total of 380 falciparum malaria patients were followed through day 28, of whom 222 were in the intervention group (artesunate + mefloquine) and 158 in the placebo group (artesunate and paracetamol). Table 1 summarizes the results.

All patients were followed up at home on days 7 and 28 by the local health assistants. On day 28, only one patient in the mefloquine group and seven in the paracetamol group remained slide-positive for *P. falciparum*. These were regarded as treatment failures. The failure rate for mefloquine was 0.45% (95% CI = 0.0–2.5) and for paracetamol (placebo) 4.4% (95% CI = 1.8–9.0). The result is statistically significant (Fisher's test, $P = 0.01$).

No patient in either group developed severe or complicated malaria, nor were any toxic effects shown. One patient from each group was hospitalized — in the mefloquine group due to giddiness and vomiting; both patients completed their treatments in the hospital and recovered fully. Another five patients from the mefloquine group complained of giddiness but required no medical intervention.

Compliance was measured by urine tests for chloroquine and quinine (used as biological markers) and by asking to see the blister packs following treatment. The compliance rate (full course of treatment) for both groups was 99.5% (378/380), only one patient in each group failing to complete the full treatment (negative urine test).

Discussion

The above results suggest that blister packs are highly acceptable (close to 100% acceptance) to

malaria patients and to dealers at the township level. It would appear that the combined packaging of drugs promoted their purchase by patients, compared with recommendations for independently purchasing two or more drugs with explanations of why multidrug therapy is important. In the subsidized mefloquine intervention described above, multidrug purchases and compliance with therapy, without blister packs, was less than 5%.

At the RHC (community) level, blister packs improved purchases and treatment compliance to nearly 100%. This has important implications for areas with increasing levels of multidrug-resistant *P. falciparum* malaria, e.g. in the Thai–Myanmar border areas and nearby townships, where the management and control of malaria are a major problem. Since artemisinin derivatives are readily available in some townships near the Thai–China border area, misuse can further increase resistance to them. In addition, the first study above has shown that health personnel, including physicians, prescribed artemisinin derivatives with incorrect dosages.

One question that remains unanswered is the impact of giving proper dosing instructions, like those in our blister packs. Our study provided both verbal and written instructions, and the blister packs were sold at a subsidized price. The price incentive could probably be discounted because a similar incentive for mefloquine was offered in the subsidized mefloquine intervention with little effect. However, the impact of clear verbal instructions from the health provider to the patient and of simple written instructions has yet to be investigated independently of the advantages of using the blister pack.

In the present study, the cure rate with artesunate, alone or in combination with mefloquine, was shown to be >95% for uncomplicated *P. falciparum* malaria. Other studies, showing high recrudescent rates (>40%), were carried out in hospitals where the patients received immediate treatment with other antimalarials that may have affected the outcome. As our study was community-based with patients who were unfamiliar with artemisinin derivatives, their compliance and response to the drug or drug combination may have been higher.

Conclusion

The combination of artesunate + mefloquine in a blister pack, which was sold at full price, showed improved drug compliance and therapeutic effect, compared with artesunate alone. However, two points should be mentioned. First, as our patients took a complete 5-day regimen of artesunate, alone or in combination with mefloquine, a comparison of the difference in the efficacy of 3-day and 5-day courses cannot be made. This matter is now being studied. Second, treatment of *P. falciparum* malaria with artesunate, alone or in combination with mefloquine, should be reserved for slide-confirmed rather than clinically diagnosed cases.

Résumé

Traitement communautaire du paludisme à falciparum non compliqué au Myanmar: influence du conditionnement sous plaquette thermoformée sur l'efficacité de l'association artésunate + méfloquine par comparaison avec l'artésunate seul

On a effectué trois études afin de déterminer la nécessité, l'acceptabilité et l'efficacité d'une adjonction de méfloquine au traitement de première intention du paludisme à falciparum non compliqué par les dérivés de l'artémisinine (DA). Une étude rétrospective portant sur 255 agents de santé de base a montré que le fait de recommander des dérivés de l'artémisinine aux malades dépendait de leur niveau de formation. Aucun des intervenants paramédicaux ni aucune sage-femme ne les a prescrits et seuls 9% des 129 médecins l'ont fait, personne n'ayant conseillé l'association DA plus méfloquine; 72% des malades ont pris des traitements trop courts pour permettre une guérison parasitologique. Afin de promouvoir l'adjonction de méfloquine aux schémas thérapeutiques préconisant les DA, nous avons organisé des ateliers d'intervention avec les prestateurs de soins de santé et assumé le coût de la méfloquine pour les malades. Dans la deuxième étude, nous avons interrogé 200 malades avant et après l'intervention afin d'évaluer l'observance des doses complètes de DA et l'utilisation de la méfloquine qui leur était offerte. Après l'intervention nous nous sommes aperçus que seuls 3,6% d'entre eux avaient utilisé la méfloquine et que 62% avaient pris des doses non curatives de DA. Dans la troisième étude, nous avons fourni des doses quotidiennes de médicaments sous plaquettes thermoformées ("blister") et avons comparé la prise de DA + placebo (158 malades) à celle de DA + méfloquine (222 malades) pendant 5 jours. Pour ces deux schémas thérapeutiques, l'observance a été de 99%. Les gouttes épaisses au 28e jour ont montré un sujet positif dans le groupe ayant reçu un DA +

méfloquine contre 7 dans le groupe DA seul. Nous en avons conclu que le fait de fournir des doses quotidiennes sous plaquettes thermoformées permet d'améliorer de façon très sensible l'observance des traitements de courte durée par des associations médicamenteuses, même si l'accroissement d'efficacité de l'association dans cette étude particulière effectuée au Myanmar est resté marginal.

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